510(k) SUBSTANTIAL EQUIVALENCE DETERMINATION
DECISION SUMMARY

A. 510(k) Number:
K033036

B. Analyte:
CA 15-3

C. Type of Test:
Quantitative

D. Applicant:
Beckman Coulter, Inc.

E. Proprietary and Established Names
BR Monitor and BR Monitor Calibrators on the Access® Immunoassay Systems

F. Regulatory Information:

1. Regulation section:
   21 CFR § 866.6010, Tumor Associated Antigen Immunological Test System
   21 CFR § 862.1150, Calibrator

2. Classification:
   Class II

3. Product Code:
   MOI (Tumor Associated Antigen Immunological Test System)
   JIT (Calibrator, secondary)

4. Panel:
   82

G. Intended Use:

1. Intended use(s):
   "The Access® BR Monitor assay is a paramagnetic particle, chemiluminescent immunoassay for the quantitative determination of CA 15-3 antigen levels in human serum and plasma using the Access Immunoassay Systems"

2. Indication(s) for use:
   "The device is indicated for use in the measurement of CA 15-3 antigen to aid in the management of breast cancer patients. Serial testing of patient CA 15-3 antigen concentrations should be used in conjunction with other clinical methods for monitoring breast cancer."

3. Special condition for use statement(s):
   For prescription use only.

4. Special instrument Requirements:
   The BR Monitor and BR Monitor Calibrators are to be used with the following Access® Immunoassay Systems: Access 1, Access 2, Synchron LXi 725, and UniCel Dxl 800.

H. Device Description:

The Access® BR Monitor assay is a two-site immunoenzymatic ("sandwich") assay. Access® BR Monitor reagent pack, BR monitor calibrators, Access Wash Buffer, Access Substrate, and Access Sample Diluent A are designed for use with the system. [K922823: Substrate and Wash Buffer].

I. Substantial Equivalence Information:

1. Predicate device name(s):
   Abbott AxSym® CA 15-3 assay

2. Predicate K number(s):
   K963926

3. Comparison with predicate:

Similarities		
Item	Access® **BR Monitor**	**AxSym CA 15-3 K963926**
Intended Use	Quantitative measurement of tumor marker	
Indication for use	To aid in the management of breast cancer patients (monitoring)	
Antigen measured	CA 15-3	
Assay format	Dual antibody sandwich	
Sample matrix	Serum or plasma	
Antibody type	Monoclonal/monoclonal	
Differences		
Item		
Solid phase	Paramagnetic particles	Latex particles
Signal detection method	Chemiluminiscence	Fluorescence
Substrate	Lumi-Phos* 530	4-mehylumbelliferyl Phosphate
Analytical Range	0.5 - 1000 U/mL	0 – 250 U/mL

The expected values obtained with both the Access® BR Monitor and with the predicate device are similar. Representative patient populations for which there was available data for the predicate were comparable at similar cut-off points, i.e., both at the low cut-off (0 – 31.3 U/mL) or the high cut-off (60.1-20 U/mL). The sample population included healthy females < 50 years old and ≥ 50 years old, females with breast cancers stages I through IV, other types of cancer (e.g., colorectal, lung, liver, ovarian, pancreatic, uterine, cervical), and benign diseases. The number of subjects tested with the predicate device was much higher in the majority of these groups. The differences in methodology did not raise any new different questions of safety and effectiveness for the intended use, and sufficient data to substantiate the claim were provided.

J. Standard/Guidance Document Referenced (if applicable):

The submission was prepared according to the *"Guidance Document for the Submission of Tumor Associated Antigen Premarket Notification to FDA"* of September 19, 1996.

K. Test Principle

A sample is added to a reaction vessel along with mouse monoclonal anti-CA 15-3 antigen alkaline phosphatase conjugate and paramagnetic particles coated with a second mouse monoclonal anti-CA 15-3 antibody. The CA 15-3 antigen in the sample binds to the immobilized CA 15-3 antibody on the solid phase, while the conjugate antibody reacts with a different antigenic site on the CA 15-3 antigen molecule. After incubation, materials bound to the solid phase are held in a magnetic field while unbound materials are washed away. Then, the chemiluminescent substrate Lumi-Phos*530 is added to the vessel and light generated by the reaction is measured with a Luminometer. The light production is directly proportional to the concentration of Ca 15-3 antigen in the sample. The amount of analyte in the sample is determined from a stored, multi-point calibration curve.

L. Performance Characteristics (if/when applicable)

1. Analytical performance:

a. Precision/Reproducibility:

Four levels of in-house controls were assayed in duplicate for 20 days, per the recommendations of the NCCLS document EP5A (Precision Performance of Clinical Chemistry Devices) to estimate **between run** and **within run** imprecision. An imprecision of < 10%CV for concentration ranging from 14.7 to 661.8 U/mL is reported. The appropriate means, SDs, and coefficients of variation (with confidence levels) were provided.

b. Linearity/assay reportable range:

The linear range of the assay was validated using normal and abnormal specimens covering the entire reportable range of the assay in dilution recovery experiments. Replicates of four of each of six serum samples were used. The overall (average) percentages of recovery ranged between 88.9 and 112.5%. The percentage recovery increased with decreasing starting concentration in the neat sample.

c. Traceability (controls, calibrators, or method):

The BR Calibrators are required but not provided with the reagent pack. The following calibrator information was provided:

- A description of the processes for value assignment and validation
- A description of how the primary reference calibrator sets were prepared and how their performance was transferred to the individual calibrators, since there is no International Standard for CA 15-3 antigen
- A description of the process for lot verification
- Proposed labeling should conform to 21 CFR 809.10
- Package labels for the calibration kit

d. Detection limit:

The analytical sensitivity or detection limit was defined as the lowest quantity differentiated from Zero with 95% confidence intervals using a six-point calibration curve, controls and ten replicates of the Zero standard. The lowest detectable level was 0.1 U/mL and an analytical sensitivity of <0.5 U/mL is reported in the labeling.

e. Analytical specificity:
The potential for cross-reactions with a panel of 23 substances, e.g. hormones, anticoagulants, vitamins, etc., that may occur commonly along with the analyte being tested was evaluated. None of the drugs and/or compounds tested caused significant interference with the Access® BR Monitor CA 15-3 assay when added to normal serum samples.

f. Assay cut-off:
The cut-off, i.e., the upper range limit (URL), established for the Access® BR Monitor is the same as that of the AxSym CA 15-3 Assay, and similar to values found in the literature. (See section I.3 above). However, direct assay performance comparisons based on the cut-off are not appropriate in this case because the assay is not used for diagnosis. (See sections **L.3** and **L.4.b** below for explanation of the adequate interpretation of clinical results for a monitoring indication.)

g. High-Dose Hook Effect studies:
A sample at about 47,000 U/mL was tested neat (five replicates) for high dose hook effect. The sample was also serially diluted (five dilutions, two replicates) to bring the concentration into the dynamic range of the assay. The neat sample and the high-titer dilution plateaued at RULs of 21,000,000 and did not enter back into the assay calibrator curve RLU range. The data show that the assay is not affected by the high-dose hook effect up to 30,000 U/mL.

h. Stability:
Data were provided to support the proposed shelf life of the kit using the prescribed storage conditions from stability studies for the reagent open pack (56 days), reagent shelf life (projected to be 12 months, study ongoing), the calibration curve (56 days), calibrator open vial (90 days), and calibrator shelf life (projected to be 12 months, study ongoing). The recommended storage conditions are compatible with the assay in a study that followed NCCLS Guidelines H18-A2 (Handling and Processing of Blood Specimens). Optimal conditions were specified based on specimen storage stability studies.

2. Comparison studies:

a. Method comparison with predicate device:
Deming regression analysis of the results of a comparison between the Access® BR Monitor and the predicate device was performed because the devices do not demonstrate linear performance. The results of a study done with 435 samples gave a slope of 0.82 (95% CI of 0.7877 to 0.8592), an intercept of 1.92 U/mL (95% CI of -0.550 to 4.395), and an r = 0.91. In addition, no statistically significant differences were obtained in the AUC for the two assays with ROC analysis (**p** = 0.1172). The method comparison across the 0 to 250 U/mL range showed acceptable agreement between the new test and the legally marketed device.

b. Matrix comparison:
The claim is made that heparin plasma samples can be used for the Access® BR Monitor assay. Therefore, a study with the anticoagulant was

performed to show that it does not interfere with the assay. An appropriate number of matched serum and plasma specimens (N=50) were tested, which covered the working assay range. The correlation for the lithium heparin plasma vs. serum study was good (slope = 1.006, r =0.997).

3. Clinical cut-off:
   Since the Access® BR Monitor CA 15-3 Assay **is not for diagnosis,** comparing the reported clinical status against the number of samples that were either positive or negative according to the URL, i.e., cut-off, for each test is inappropriate. Instead of plotting the actual results in U/mL versus time for the graphical representation of the monitoring data, the calculated percentage change between two time points, i.e., $t_2 - t_1 / t_1 \times 100$, should be used. Based on the **percent change in CA 15-3 results from one visit to the next**, each patient can be classified as stable, progressing, or not progressing, according to the defined criteria.

4. Clinical studies:
   a. *Clinical sensitivity and specificity:*
      A total of 44 serum samples from 25 women diagnosed with breast cancer (Stages II to IV) that had a diagnosis of "progression" were tested to calculate sensitivity, and clinical specificity was calculated based on 20 samples from 11 females originally diagnosed with breast cancer (Stages II to IV) with "no evidence of disease" status, based on the 31.3 U/mL URL. Based on these data, a sensitivity of 70.5%, a specificity of 90.0%, and a 76.6% agreement are reported for the Access® BR monitor. The same comparison between the predicate device's assay results and clinical diagnosis produced similar results.

   c. *Other clinical supportive data*
      Monitoring of Patients Diagnosed with Breast Cancer
      To demonstrate clinical utility as an **aid in monitoring**, evaluations of tumor marker analytes should demonstrate that the marker is a significant predictor of changing clinical status. Therefore, the applicant tested a suitable sample of patients (N= 36) and evaluated/the predictive power of the marker against other known clinical diagnostic variables, i.e., disease stage, remission, recurrence and other conditions including prior treatment regimens. The data used to support the intended use of the device are representative because they are a sampling of the population for whose use the device is intended.

      Based on criteria reported in the published literature and on study results summarized in the labeling for similar commercially available CA 15-3 tests, **a ± 25% change in the assay value between any two consecutive points** was considered either progression (>25%), no change (0%), or remission/response to treatment (<25%). Assay results were compared with clinical status based on the 25% LSC for each device, and 25% LSC for assay results between both devices.

      The supporting information provided included 1) adequate documentation for the choice of the significant percentage of clinical change with copies of reference articles from the published literature, 2) tabulation and line

item data listing of patients according to their estimated percentage change with the corresponding clinical status per test, 3) graphs of the monitoring data for each patient (4 data points), 4) an assessment of the comparison between the results obtained with each device and clinical diagnosis, and between both devices based on the estimated percentage change, and 5) an assessment of sensitivity and specificity for the assay monitoring results, according to the chosen clinically significant percentage.

5. Expected values/Reference range:

Normal Individuals
Number of Subjects: Sera from apparently healthy males (N=43) and females (304) were tested with the Access BR Monitor and with the predicate test device (at an external reference laboratory). The distribution of values among healthy females was very similar with both assays.

	N	ACCESS BR MONTIOR		AXSYM	
		Mean CA 15-3 U/ML	SD	Mean CA 15-3 U/ML	SD
Females	304	12.2	5.7	14.4	6.2
Males	43	15.0	6.5		

The total concordance was 99% (301/304). Three discrepant samples were observed, i.e., two with the predicate and one with the BR Monitor device. The device results correlate well using linear regression (slope close to 1.0 and intercept close to zero) with a method that has a published reference range for healthy individuals.

M. Conclusion:

The 510(k) submission complies with all of the required administrative documentation, i.e., a 510(k) statement [as required in 21 CFR 807.93 (a)], a 510(k) Truthful and Accurate statement [as required by 21 CFR 807.87(k)], and the Indications for Use statement [as required by 21 CFR § 807.92 (a) (5).] In addition, the document contained relevant device-specific literature references, complete information about the characterization of the antibodies used in the assay, and the recombinant/monoclonal methodology used. Device labeling complies with Section 502(a) of the Act, and follows 21 CFR § 807.87 (e) and 21 CFR 809.10 for requirements for labeling of *in vitro* diagnostic products.

The purpose of this 510(k) was to request clearance for an *in vitro* diagnostic device called the BR Monitor and BR Monitor Calibrators on the Access® Immunoassay Systems for the quantitation of CA 15-3 in serum and plasma.

The performance of the device has been established by comparison to a legally marketed medical device with the same intended use. Therefore, the analytical and clinical information provided in this submission demonstrate that the BR Monitor and BR Monitor Calibrators on the Access® Immunoassay Systems is substantially equivalent to a device legally marketed in the United States for the specific intended use and the clinical indication, i.e., monitoring of breast cancer patients.